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Cisplatinum and Interstitial Laser Therapy for Advanced Head and Neck Cancer: A Preclinical Study

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Background and Objective: **Direct intratumor injection of cisplatinum (CDDP) and laser therapy were tested for improved treatment of squamous cell carcinoma (SCCA).**
Study Design/Materials and Methods: **Human SCCA tumors were grown as sc transplants in nude mice and injected with CDDP (0.4–1.2 mg/gm) in water or in collagen-based gel carrier with epinephrine (epi-gel), followed by interstitial laser therapy (ILT) via 0.6 mm fiberoptics (532 nm/300J).**
Results: **Tumors injected with CDDP epi-gel exhibited a partial response with 2–4-fold tumor growth delay, compared to aqueous drug or untreated SCCA transplants during 10-week follow-up. Combined drug and laser therapy significantly decreased tumor volume with recurrence in only 25% (2/8) of animals tested, compared to 66% tumor regrowth (10/15) after ILT alone.**
Conclusion: **These initial results suggest laser chemotherapy may become an effective treatment for advanced head and neck cancer. Lasers Surg. Med. 21:423–431, 1997.**

Key words: cisplatinum; interstitial laser therapy; squamous cell carcinoma

INTRODUCTION

Advanced squamous cell carcinoma of the head and neck has a 50–60% recurrence rate within 5 years after surgical excision, radiation treatment, or chemotherapy [1,2]. More effective treatment should be possible by intraoperative combination therapy [1]. Use of the chemotherapeutic agent cisplatinum (CDDP) as an adjunct in the treatment of advanced head and neck cancer has shown promising response rates [3,4]. However, the effects of CDDP on long-term survival remains controversial, and tumor chemotherapy has been limited by systemic side effects includ-

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ing gastrointestinal toxicity, myelosuppression, and nephrotoxicity [5]. In addition, prior irradiation or surgery at the target sites contribute to poor tissue vascularity, resulting in decreased intratumor CDDP levels [6]. Previous efforts to improve local tumor response and minimize systemic side effects by injecting CDDP directly into tumors have not been effective, since hematogenous diffusion of the drug appears to rapidly diminish intratumor drug levels [6–8]. In an effort to prolong high intratumor drug levels, CDDP recently has been combined with epinephrine in a collagen gel as an intralesional therapeutic vehicle [9].

Reports from several investigators indicate tumor cytotoxicity of CDDP is enhanced by local or systemic hyperthermia [10]. Heat also appears to partially reverse acquired resistance to CDDP at temperatures above 42°C [11]. Drug toxicity is increased by heat in tumor cells, and also leads to elevated drug-sensitivity in surviving cells [12]. Several sources of energy have been used for tumor hyperthermia. These include heated water, electromagnetic energy at radio and microwave frequencies, sonic energy from ultrasound, and infrared light from heat lamps. Each of these techniques produces non-uniform tumor heating and thermal damage to adjacent normal tissues, which has been a significant limitation [13]. Interstitial laser therapy (ILT) delivered via submillimeter fiberoptics is a less invasive method to produce localized hyperthermia focused in the treatment site. KTP-532 and Nd:YAG lasers are currently used clinically for ILT in a number of human malignancies [13–14].

To our knowledge, there have been no reports from either experimental models or clinical trials on combined therapy with CDDP in a gel vehicle coupled with local hyperthermia delivered via laser fiberoptics. In order to test the feasibility and efficacy of this treatment methodology, nude mice bearing subcutaneous transplanted human squamous cell carcinoma (SCCA) tumors were injected intralesionally with CDDP alone or with CDDP in gel. Four hours after drug injection, a KTP/Nd:YAG laser was used to deliver continuous wave green light of 532 nm at 0.8 W, via a 0.6 mm fiberoptic cable implanted interstitially in multiple tumor sites. Combined therapy resulted in nearly complete tumor ablation and a significantly decreased recurrence rate compared to the drug or laser alone.

MATERIALS AND METHODS

In Vitro Culture of Human Squamous Cell Carcinoma

The UCLA-SO-P3 cells were established in culture from a pulmonary squamous cell carcinoma derived from a 53-year-old, white male of red blood cell type A. The P3 cell line was maintained at 37°C in a CO_2 humidified atmosphere as monolayers in culture flasks containing RPMI-1640 medium supplemented with 10% fetal calf serum (GIBCO, Grand Island, NY), 2 mM L-glutamine (GIBCO), 20 mM HEPES buffer pH-7.4 (Irvine Scientific, Irvine, CA), 50 μg/ml gentamycin (Irvine), and 0.5 μg/ml fungizone (JRH, Lenexa, KS).

In Vivo Tumor Model

Balb/c nu/nu mice 6–8 weeks old were maintained in filter top sterile plastic cages. P3 tumor cells were detached from monolayer cultures with 0.25% trypsin and viable cells counted in trypan blue using a hemocytometer slide before subcutaneous injection in the posterior flank at 1×10^7 cells/0.1 ml of RPMI media. Palpable tumors were present in 95% of the animals within 7–10 days. Tumor volume was measured with vernier calipers using the formula $V = 2/3\ (L \times W \times H)$. P3 tumors required approximately 4 weeks to grow to a size of 400–600 mm^3, presenting little central necrosis and a good vascular supply at the time treatment was administered. Animals were weighed, tumors measured, and photographed weekly throughout the entire follow-up period of 10 weeks.

Laser Light Delivery and Treatment

Interstitial laser energy was produced by a KTP/Nd:YAG crystal laser (Laserscope, San Jose, CA) set to deliver continuous wave green light at 532 nm, with a power output of 0.8 W via a 0.6 mm fiberoptic cable. The animals were first anesthetized by an intraperitoneal injection of nembutal in ethanol. ILT was performed on sedated animals with 400–600 mm^3 tumors by fiberoptic implantation through the skin into the tumor. Laser energy was delivered to multiple tumor sites in a circumferential pincushion technique by activating the KTP laser for 5 sec/site at the periphery and 5 sec for each 2.5 mm depth in the tumor center. Interstitial fiberoptic implantation sites were spaced at 4 mm intervals over the lesion, including tumor margins, while maintaining a ra-

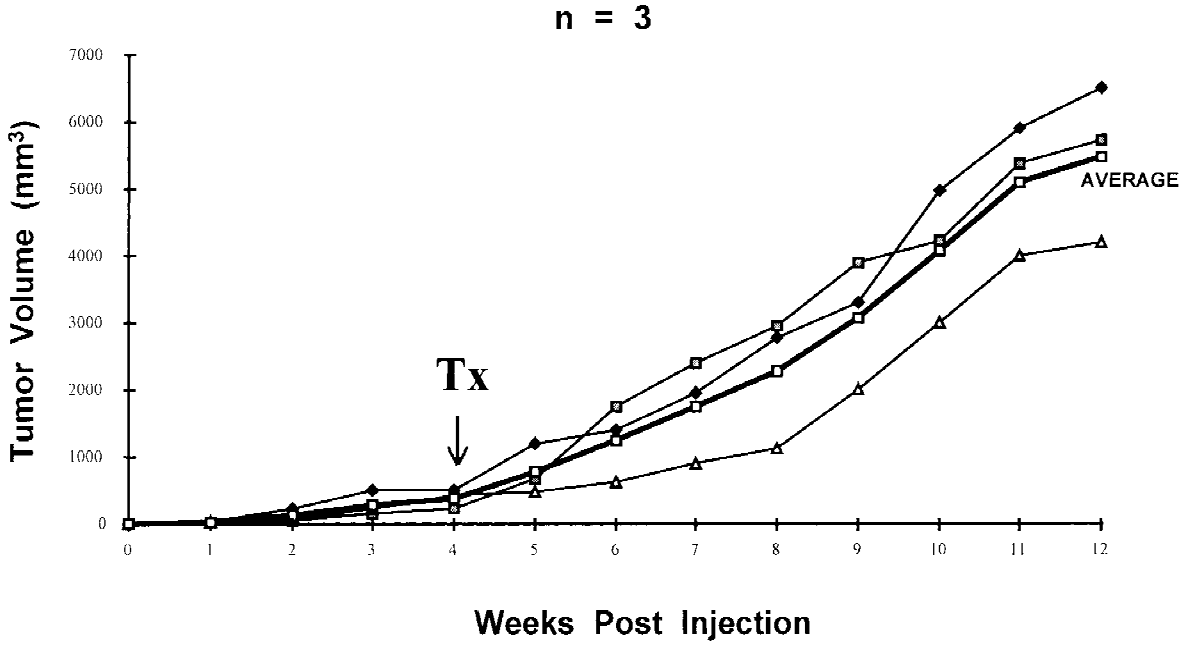

Fig. 1. Growth of human SCCA squamous cell carcinoma tumors transplanted subcutaneously in nu/nu mice.

tio of total energy delivered to the tumor volume of 1.5 J/mm^3, as previously described [15,16].

Thermal monitoring of ILT was performed with a high speed BAT-12 interstitial thermal probe to measure tumor temperature profiles during bare fiberoptic insertion and low energy (13.5 J/cm^2) therapy in 5 animals.

Intratumor CDDP Injections and ILT

For CDDP/epi gel intratumor treatment, suspensions of CDDP at 1 mg/ml and 3 mg/ml in sterile water were prepared with epinephrine (0.1 mg/ml) and 20 mg/ml purified bovine collagen, as provided by Matrix Pharmaceutical, Inc. (Fremont, CA) Injection volume was determined by the formula I = 3/8(V) where V equals tumor volume. This resulted in a maximum drug dose of 0.375 mg and 1.225 mg/gm of tumor. However, drug reflux through the skin puncture was noted in some cases and led to reduced intratumor drug doses. For the combined treatment group (CDDP/epi gel + KTP), the laser treatment was performed 4 hours after drug injection, and animals were observed for a 10-week follow-up.

RESULTS

Interstitial Laser Treatment of Subcutaneous SCCA Tumor Transplants

SCCA tumor transplants with initial volumes of 400–600 mm^3 continued to grow for 10 weeks to 8-fold increased average size (Fig. 1). Laser therapy was performed on the SCCA tumors of this initial size to define a minimum energy level needed for complete tumor ablation. Following tumor treatment with 600J of KTP 532 laser output (t = 10s/site, intensity = 2.7 W/cm^2, energy density = 27 J/cm^2) via interstitial fiberoptic implantation, recurrence was observed in 2/5 cases (Fig. 2). These results resemble the recurrence rate seen clinically after ILT in head and neck cancer patients, where 40% of the patients failed to achieve local tumor control. Because ILT led to tumor ablation and a complete response by photothermal energy alone in 60% of the treated animals, the experiment was repeated in SCCA tumors with another group of 15 animals using a laser exposure time of 5 sec (power density: 13.5 J/cm^2). When using half the previous energy delivery, ILT-induced tumor regression was reduced and followed by regrowth in 10/15 cases (Fig. 3.) At this lower energy, the failure of laser alone in over half of the cases allowed us to test the feasibility of an improved tumor response after combined drug and ILT.

Temperature monitoring of ILT was performed in 5 animals. Temperature before ILT averaged T_0 = 32.1°C when the thermal needle probe was inserted at the tumor periphery. After thermal measurement, the laser was activated, and the circumferential pincushion technique was

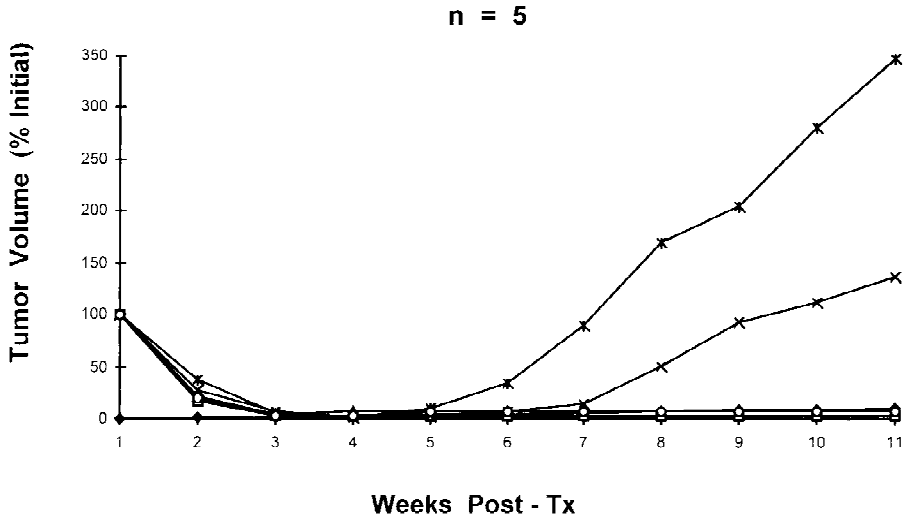

Fig. 2. Treatment response after interstitial fiberoptic KTP laser therapy of 5 SCCA tumor transplants at high power (27 J/cm^2 per site, 10 sec at 0.8 W, average: 60 sites, 600J).

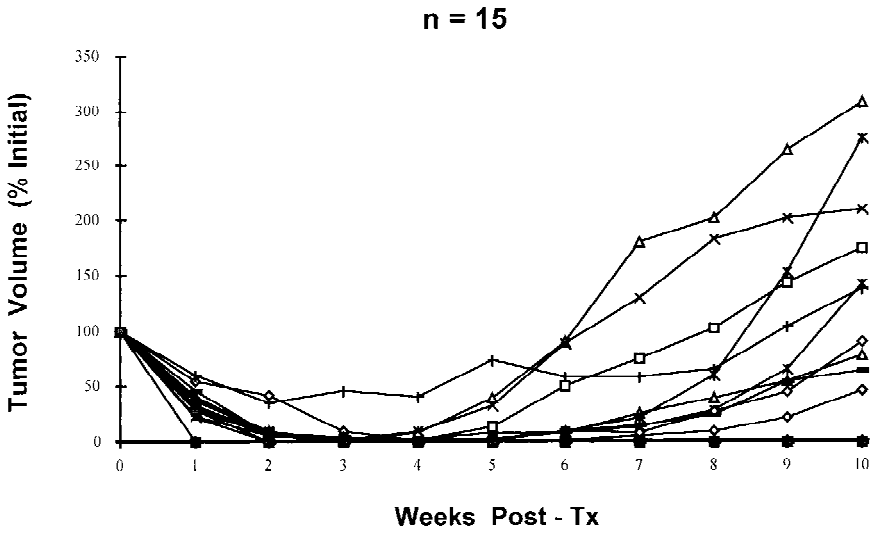

Fig. 3. Treatment response after interstitial fiberoptic KTP laser therapy of 15 SCCA tumor transplants at low power (13.5 J/cm^2 per site, 5 sec at 0.8 W, average 60 sites, 300J).

performed in a decreasing spiral from the periphery towards the center of the tumors. During ILT of these transplanted SCCA tumors, the thermal probe inserted just beyond the tumor margin reached an initial temperature of 45°C which decreased to 39.1°C at the end of the treatment session. The mean temperature recorded immediately after ILT reached a T_{MAX} of 62.5°C at the tumor center, returning to T_0 by 1 min and 30 sec (SD = ±15 sec) after a 6-min ILT session.

Intratumor CDDP and ILT

Intralesional injections of CDDP/epi gel were performed in 5 animals per group, in order to define tumor growth rate inhibition by the drug alone. Lower CDDP concentrations of 1 mg/ml (0.375 mg/gm tumor) were tested in 5 tumors, as shown in Figure 4, and compared to 3 mg/ml (1.225 mg/gm tumor), both with a 10-week follow-up (Fig. 5). SCCA tumors injected with low dose drug had reduced growth for 3 weeks, but exhibited a 4-fold increase in average tumor volume by 10 weeks (Fig. 4). High dose intralesional CDDP led to an average tumor size decrease by 3 weeks, but subsequent 2-fold increased tumor volume by 10 weeks (Fig. 5).

Because systemic toxicity was not observed in animals treated with the higher drug dose, this

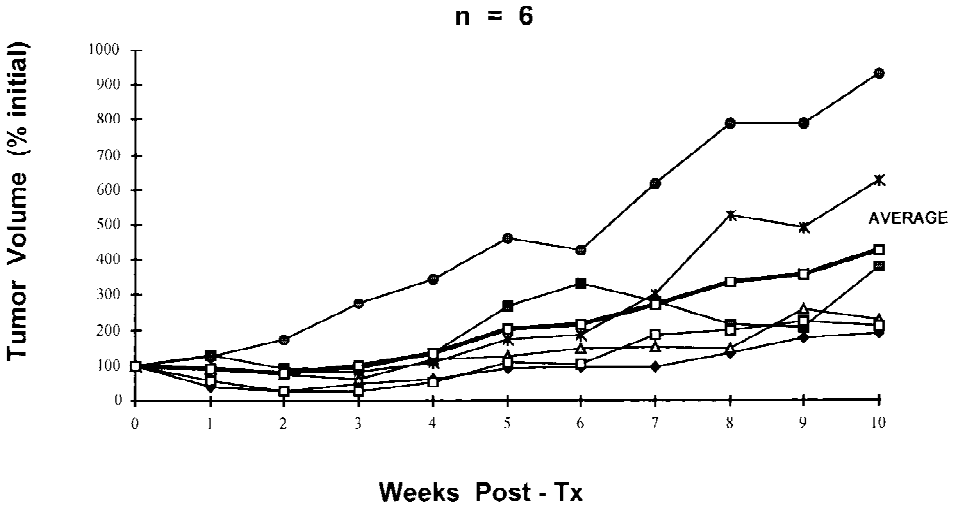

Fig. 4. Response after intratumor injection of CDDP gel (1 mg/ml) for treatment of human SCCA transplanted in 6 nu/nu mice.

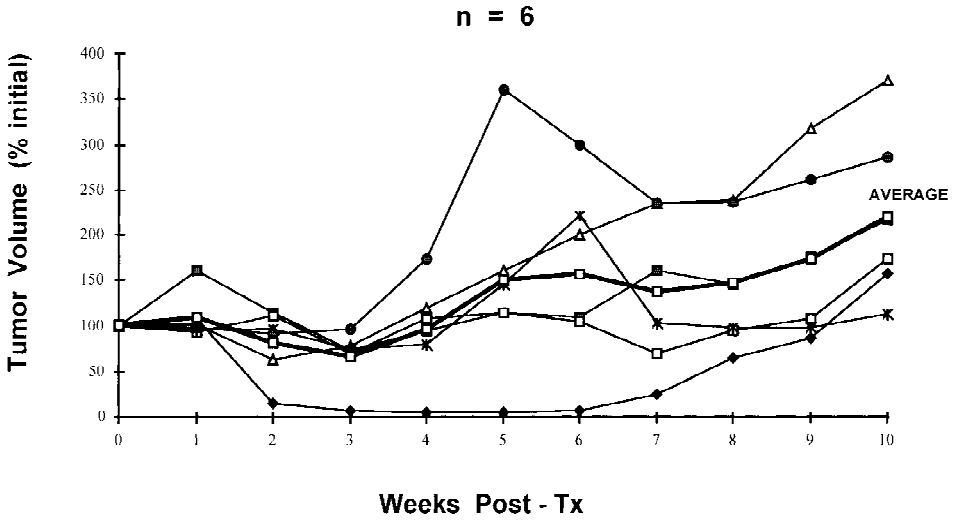

Fig. 5. Response after intratumor injection with high dose (3 mg/ml) CDDP in gel for treatment of human SCCA transplanted in 6 nu/nu mice.

CDDP level was combined with low energy ILT in the transplanted SCCA tumors. Treatment was started 4 hours after intratumor drug injection for the combined therapy group (CDDP/epi gel + KTP) in 8 animals. Combined drug and ILT led to complete tumor regression in 6/8 cases as shown in Figure 6. By comparison, only one-third of the mice (5/15) had no tumor recurrence after single modality ILT (Fig. 3). Chi square 2 × 2 analysis of these two ILT vs. laser chemotherapy treatment groups, comparing complete tumor regression (5/15 vs. 6/8), revealed a significant difference ($\chi^2_{(1)} = 5.99$, $P < 0.05$) in therapeutic outcomes. Thus, combined therapy was clearly an improvement over ILT alone for the treatment of SCCA tumors in this transplant model.

No weight loss, increased morbidity, or other indications of systemic toxicity were seen in the mice after ILT or combined therapy. The local tissue response to laser chemotherapy also appeared to be mild, as shown in Figure 7, with complete ablation seen following drug and ILT treatment. Initial response at 24 hours after therapy included edema and inflammation of the tumor. Edema then decreased with tumors containing areas of visible necrosis around each treatment site. Viable tumor was not observed but may have been obscured by necrotic tissue. At 1 week after ILT, a

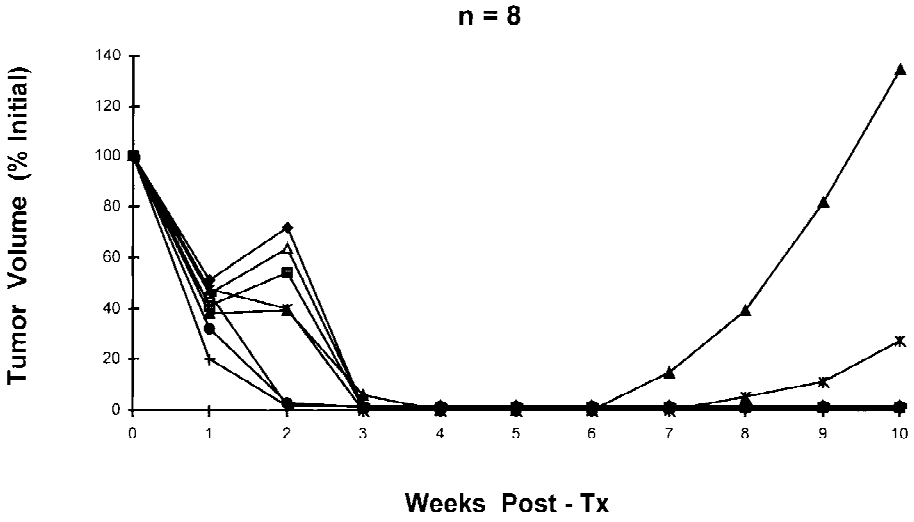

Fig. 6. Response of 8 SCCA tumor transplants after injections of high dose intratumor CDDP gel followed by interstitial fiberoptic KTP laser therapy at 320J.

dry scab formed which was slowly replaced by granular tissue and fibrosis after 2 weeks. Tumor regrowth was observed, in 2 cases, by 6 weeks after ILT, only at the margin of the original tumor, with the combined treatment area containing a hypertrophic scar. The results suggest laser chemotherapy is minimally invasive and well tolerated in this SCCA tumor transplant model.

DISCUSSION

Cisplatinum is a potent cytotoxic agent used for therapy in a wide range of tumors, including cancer of the head and neck. Although this drug has become one of the most widely used cancer chemotherapeutic agents, renal toxicity and other side effects have limited its application [5]. Despite encouraging tumor response rates after treatment with CDDP and other chemotherapeutic agents, the lack of significant improvement in survival of patients with advanced head and neck cancer suggests a need for improved drug delivery to the target tumor [6]. Intravenous drug delivery to tumors is compromised by systemic toxicity and reduced uptake due to local devascularization after surgery or radiation therapy, as well as high interstitial pressure from rapid tumor growth [6]. Intralesional injections of free CDDP have been compromised by an inability to maintain high intratumor drug levels for a time interval sufficient to maximize intracellular uptake [7,8].

The primary goal of local chemotherapy is to improve local control by increasing the dose of drug to which malignant cells are exposed [17]. In an effort to prevent rapid drug redistribution away from the site of intratumor administration, various drug carrier formulations have been investigated, including liposomes, magnetic albumen microspheres, oil/water emulsions, and, more recently, bovine collagen gels [9]. By combining CDDP with collagen as a protein carrier, and epinephrine as a vasoconstrictor, higher intratumor drug levels can be maintained for up to 24 hours using CDDP/epi gel [17].

A multicenter study of intralesional injection using cisplatin in 45 patients with advanced malignant tumors of the head and neck indicated that the incidence of adverse effects and clinical toxicities were minimal following administration of CDDP in an epinephrine collagen gel. This study also showed intralesional drug injection in gel was feasible, and resulted in an objective clinical response in 50% of the patients. A dose of 2mg CDDP/cm^3 tumor was well tolerated, contributed to tumor responses, and provided a dose which adequately infiltrated tumors [18].

Preclinical reports indicate that CDDP is a strong thermal sensitizing drug, with evidence from both cell culture and animal models confirming this marked sensitization [10–12,19]. Cisplatinum also is among the best anticancer drugs for clinical combination therapy with radiation treatment [20]. For example, CDDP has been used with various protocols in an attempt to sensitize tumors for external beam radiotherapy, particularly in head and neck cancers with an acceptable clinical toxicity profile [21,22].

Hyperthermia (HT) also has been reported to

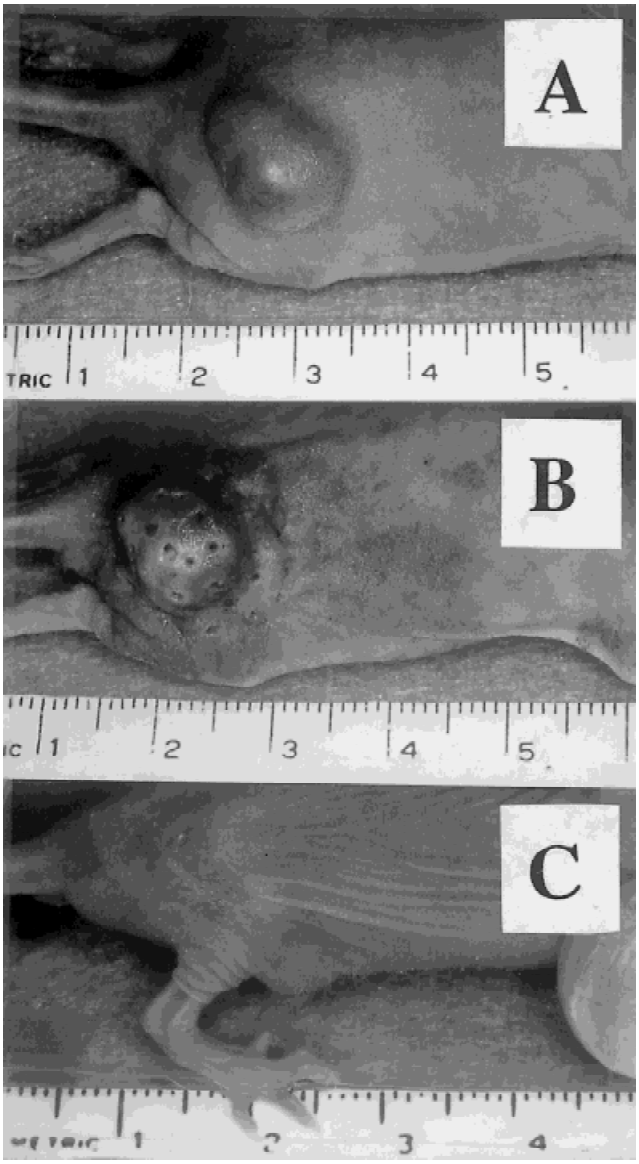

Fig. 7. SCCA tumor appearance prior to and following CDDP gel and KTP laser (320J) treatment. **A:** Before therapy; **B:** Immediately after ILT; and **C:** 12 weeks after drug and ILT.

enhance the tumoricidal response after irradiation, and after chemotherapy with several agents including CDDP [19]. In particular, HT enhances the activity of CDDP by potentiating tumoricidal effects progressively as temperatures are elevated to 43°C leading to supra-additive lethal effects [23]. Evidence indicates that heat induction leads to ultrastructural changes in cell membranes, leading to increased drug toxicity and altered cellular metabolism [24,25]. This altered metabolism and inhibition of DNA repair mechanisms at elevated temperature improves tumoricidal effects [26,27]. This CDDP thermal enhancement would be expected to occur near the tumor margin in the current study at 45°C, rather than at the tumor center where coagulation occurred after ILT at temperatures over 60°C.

The selection of dose, drug vehicle, and schedule for intratumor chemotherapy are not only important factors for the efficacy of combined therapy with cisplatin and laser, but also key elements in determining tolerance to treatment [28]. Hahn initially reported a synergistic effect when CDDP (2 mg/kg) was administrated 24 hours prior to hyperthermia (43°C/30 min) and near-maximum effects were observed when both modalities were carried out simultaneously [19]. Kitamura et al. demonstrated that regional injection of CDDP, followed by local hyperthermia, led to 6-fold decreased tumor growth rate of murine melanoma and improved prognosis without renal drug injury or the promotion of hematogenic metastasis [29]. Intratumor administration of CDDP led to animal weight gain in this study, but systemic injections of the drug led to significant weight loss or absence of weight gain.

Previous investigations with a murine fibrosarcoma model confirmed that cisplatin was an ideal drug with which to begin chemothermal therapy, and that the sequence of cisplatin hyperthermia, followed by radiation treatment, was highly effective [19,20,22]. Based on earlier studies showing substantial diffusion of cisplatin from a slow release gel in murine models by 4 hours, the current study employed this time for CDDP injections before interstitial laser application [17].

Results of the current study show that both CDDP/epi gel groups treated with 1 mg/ml and 3 mg/ml induced a delayed growth of SCCA tumors compared to untreated control tumors. Combined treatment with high dose CDDP/epi gel and low energy ILT resulted in a significantly improved outcome ($P < 0.05$ by χ^2), with 6/8 complete tumor regressions and only 2/8 late recurrences over a 12-week follow-up, compared to ILT alone with 10/15 tumor recurrences. Most recurrences seen in the ILT alone and the laser chemotherapy combined treatment group appeared at the margin of the original tumor site. This outcome may be related to insufficient ILT treatment, since the pincushion technique was performed in a spiral beginning at the margin of the tumor and moving towards the center. When ILT treatment was initiated, temperature at the tumor margin averaged 45°C, in contrast to the tumor core where a temperature of 62.5°C was seen immediately after laser therapy. With the ILT spiraling tech-

nique in a centripetal direction, increased temperature levels in the central area reflect a higher density of laser energy. This most likely accounts for the recurrences seen at the tumor margin where less thermal energy was delivered. After combined therapy, recurrence was seen in 2 of 8 animals (25%), compared to 10 of 15 (66%) treated with ILT alone. In similar experiments, Sakurai combined different time schedules of 5-Fu chemotherapy before and after hyperthermia to show that hyperthermia 2 hours after drug administration was the most effective treatment, which correlated with higher drug levels in tumors as measured by high performance liquid chromatography [30].

The most common biologic effect of interstitial laser energy deposition is thermal damage. Interstitial laser therapy in tumors leads progressively to protein denaturation, coagulation, vaporization, and carbonization with increased temperature modifying the microscopic tumor environment [13]. Microvascular and interstitial pressure after ILT thermal coagulation in the tumor core region could increase redistribution of the drug into tumor cells at the margin, potentiating the combination of laser and drug therapy [30].

Long-term remission and tumor eradication may be enhanced by combining intratumor chemotherapy with photothermal energy delivery via laser fiberoptics. Further improvements are possible in laser energy delivery using diffuser tips for more consistent intratumor heat distribution and better drug activation at the margin. The results of the current investigation provide the first evidence that CDDP and KTP laser fiberoptics can be combined for more effective tumor therapy in a preclinical model, although the mechanism involved has not been defined.

CONCLUSION

The effectiveness of combination chemo and radiation therapy in treatment of human cancer suggests a need for further development of new multimodality approaches including laser photochemotherapy. The preclinical results presented in the current study indicate that direct intratumor injection of CDDP in a collagen gel, followed by KTP laser fiberoptic energy delivery, can induce a more improved therapy response than either modality alone. Further studies to define optimal laser energy and drug delivery system will be necessary before clinical application.

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